REMARKS

Status of Claims

Applicants have amended claim 1, and claims 9-50 have been withdrawn from examination at this time. As a result, claims 1-53 are currently pending; however, claims 1-8 and 51-53 are now under examination in this application. No new matter has been added to the claims.

Support for the amendment to claim 1 can be found throughout the specification. For example, support for the phrase "residues involved in unfavorable electrostatic interactions" can be found at page 37, line 6 through page 38, line 13 of the specification.

Rejection of Claims under 35 U.S.C. §112

The Examiner rejected claims 1-8 under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner indicated that claim 1 is indefinite in the recited "wherein the stabilizing mutation removes and unfavorable electrostatic interaction in the Fn3." Claim 1 has been amended to remove this phrase. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection of Claims under 35 U.S.C. § 102(b)

The examiner rejected claims 1-2, 6, 8 and 51 as being anticipated under 35 U.S.C. § 102(b) by Koide (WO 98/56915) and Lipovsek (WO 00/34784).

Page 3 of the Office Action states that page 10, line 3 of WO 98/56915 recites that the mutated polypeptides result in the stabilization of TSAC. When read as a whole, page 10 of WO 98/56915 discloses preparing an Fn3 polypeptide monobody, contacting the polypeptide monobody with a second compound (TSAC), determining the binding structure of the polypeptide:TSAC complex, and preparing a variegated nucleic acid library such that the polypeptide has improved binding to or stabilization of the TSAC. Thus, this passage discloses a

way of improving the stabilization of the TSAC, but does not teach the stabilization of the Fn3 polypeptide monobody.

Page 3 of the Office Action further states that page 5, line 26 to page 6, line 10 of WO 98/56915 implicitly discloses that "the Fn3 is stable relative to the disulfide containing Fn3." This passage of WO 98/56915, however, discusses tendamistat, which is an amylase inhibitor, and not Fn3. Tendamistat is a completely different molecule than Fn3. This passage of WO 98/56915 does not discuss Fn3 at all. Further, it should be noted that Fn3 does not contain disulfide bonds.

Page 4 of the Office Action states that the procedure for making an Fn3 molecule with a stabilizing mutation is described by Koide in Example XVI by measuring the pH. Pages 50-51 of WO 98/56915 discuss the solubility of Ubi4 and Ubi4-Fn3. This passage does not, however, discuss the stability of these proteins. Thus, Example XVI of WO 98/56915 does not teach a modified Fn3 containing a stabilizing mutation of one or more residues involved in unfavorable electrostatic interactions, as recited by the pending claims.

Further, page 4 of the Office Action asserts that Example XVI of WO 98/56915 states that "Ubi4-K proteins remain comparable to that of the typical globular protein." Applicant believes that the examiner intended to refer to Example XVII of WO 98/56915 (page 53, lines 14-16), which states: "Though the introduced mutations in the two loops certainly decreased the stability of Ubi4-K relative to wild-type Fn3, the stability of Ubi4 remains comparable to that of a 'typical' globular protein." It is true that the Ubi4-K proteins with mutations in the loops recited in WO 98/56915 had stabilities comparable to typical globular proteins. The proper comparison of the presently claimed modified Fn3 molecule having a stabilizing mutation is to a wild-type Fn3, and not to a "typical globular protein." Wild-type Fn3 is more stable than typical globular proteins, and the claimed modified Fn3 is even more stable than wild-type Fn3.

Page 5 of the Office Action states that Lipovsek at page 19, lines 13-14 discloses that the mimics possess stability properties superior to antibodies. Applicant asserts, however, that the proper comparison is between a wild-type Fn3 and the modified Fn3 recited by the claims, and not between Fn3 and an antibody, which is an entirely different protein. Further Lipovsek does

not teach or suggest modified Fn3 molecule, wherein the Fn3 has a stabilizing mutation of one or more residues involved in unfavorable electrostatic interactions as compared to a wild-type Fn3, as recited by the present claims.

Page 5 of the Office Action states that "the procedure of removing an unfavorable electrostatic interaction in the Fn3 that results in a stable Fn3 is inherently taught by Lipovsek. Such unfavorable interactions have to be inherently removed in order for the Fn3 compound to remain stable." Applicant disagrees with the statement that unfavorable interactions have to be removed in order for a compound to remain stable. For example, *Bacillus subtilis* CsbB protein contains a highly unfavorable electrostatic interaction between Glu3 and Glu66, but this protein is still predominantly folded at physiological temperature (Perl *et al.*, 2000, *Nature Structural Biology*, 7, 380-383).

Page 5 of the Office Action states that Koide (WO 98/56915) teaches the stability of Fn3 as specifically disclosed in Example XVI, which should remain stable when involved in binding activity, and that Lipovsek (WO 00/34784) also discloses that the Fn3 mutant has to be stable relative to the wild type to be physiologically useful. As discussed above regarding Koide (WO 98/56915), however, the proper comparison of the presently claimed modified Fn3 molecule having a stabilizing mutation is to a wild-type Fn3, and not to a "typical globular protein" as discussed in Example XVII of WO 98/56915. Wild-type Fn3 is more stable than typical globular proteins, and the claimed modified Fn3 is even more stable than wild-type Fn3. Regarding Lipovsek (WO 00/34784), nowhere does Lipovsek teach that an Fn3 mutant has to be stable relative to the wild type to by physiologically useful. As discussed above, Lipovsek merely discloses that the mimics possess stability properties superior to antibodies. Again, the proper comparison that needs to be made is between a wild-type Fn3 and the modified Fn3, as recited by the claims. Further, Lipovsek does not teach or suggest modified Fn3 molecule, wherein the Fn3 has a stabilizing mutation of one or more residues involved in unfavorable electrostatic interactions as compared to a wild-type Fn3, as recited by the present claims.

Regarding the examiner's comments on page 6 of the Office Action, Applicant does not agree with the examiner's assertion of the teaching of Lipovsek and the modules of Fn3.

However, in order to expedite prosecution, claim 1 has been amended to recite the mutation of one or more residues involved in unfavorable electrostatic interactions, thereby overcoming this rejection.

In conclusion, neither Koide (WO 98/56915) or Lipovsek (WO 00/34784) disclose a modified Fn3 that, as compared to a wild-type Fn3, has a stabilizing mutation of one or more residues involved in unfavorable electrostatic interactions (as recited by the pending claims). Since neither Koide (WO 98/56915) or Lipovsek (WO 00/34784) anticipate the claimed subject matter, and Applicant respectfully requests withdrawal of this rejection of claims 1-2, 6, 8 and 51 under 35 U.S.C. § 102(b).

Rejection of Claims under 35 U.S.C. § 103(a)

The examiner rejected claims 1-3, 5-6, 8 and 51-53 as being anticipated under 35 U.S.C. § 103(a) by Koide (WO 98/56915) or Lipovsek (WO 00/34784) in view of Blaschuk (US 6,391,855).

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the cited reference itself or in the knowledge generally available to an art worker, to modify the reference so as to arrive at the claimed invention. Second, there must be a reasonable expectation of success, *i.e.*, that the invention would be operable. Finally, the prior art reference must teach or suggest all the claim limitations (M.P.E.P. § 2143). The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure (M.P.E.P. § 2143, citing with favor *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

Page 7 of the Office Action states that it would be within the ordinary skill in the art to determine whether a substitution affects the stability of the mutant Fn3, and that one having ordinary skill in the art would have known that positively charged residues such as Lys or Arg are known to have stabilizing effect on molecules such as Fn3 as taught by Koide (WO 98/56915).

First, Applicant disagrees that the substitution of positively charged residues for other residues would necessarily have a stabilizing effect on a protein. Applicant asserts that a change in charge of individual amino acid residues would have differing effects proteins, all of which have unique conformational environments. For example, Dao-pin, S., Sauer, U., Nicholson, H. & Matthews, B. W., "Contributions on engineered salt bridges to the stability of T4 Lysozyme determined by directed mutagenesis." *Biochemistry* 30, 7142-7153 (1991) teach that the introduction of an attractive electrostatic interaction has small effects on protein stability. Second, applicant concedes that one of ordinary skill in the art would have been able at the time that the application was filed to perform substitutions in a protein, and to determine whether the modified protein was more stable that the wild type application. Applicant asserts, however, that the cited art does not contain a suggestion or incentive that would have motivated the skilled artisan to modify the references. The Federal Circuit in *In re Sang Su Lee*, 61 U.S.P.Q.2d 1430-1436, 1433 (Fed. Cir. 2002) stated the following:

> The factual inquiry whether to combine references must be thorough and searching. . . . [i]t must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. See, *e.g.*, *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 U.S.P.Q.2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting C.R. Bard, Inc., v. M3 Systems, Inc., 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined *only* if there is some suggestion or incentive to do so.'") (emphasis in original) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984)).

The Examiner is urged to consider that there is no teaching in the cited references to modify Fn3 in order to generate a stabilizing mutation of one or more residues involved in

unfavorable electrostatic interactions as compared to a wild-type Fn3 molecule (as recited by claims 1-3, 5-6 and 51-52), or to generate a stabilizing mutation that increases the Fn3 molecule's melting point by more than 0.1°C as compared to an Fn3 molecule that is identical except for the stabilizing mutation (as recited by claim 53). Until the inventor performed the experiments disclosed in the present specification, it was not known if one could successfully make a more stable Fn3. Thus, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Withdrawal of the rejection of claims 1-3, 5-6, 8 and 51-53 under 35 U.S.C. § 103(a) is therefore respectfully requested.

Allowable Subject Matter

The examiner has indicated that claims 4 and 7 would be allowable if incorporated into claim 1.

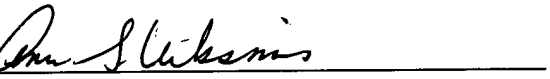
Conclusion

Applicants respectfully submit that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (612) 337-2540 to facilitate prosecution of this application.

Enclosed herewith is a Petition for a Three-Month Extension of Time. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 2 April 2004



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